

Deuterium Nuclear Magnetic Resonance. Evaluation of the Positional Distribution of Low Levels of Deuterium in the Presence of $\text{Eu}(\text{fod})_3$

Summary: ^2H NMR spectroscopy, in conjunction with the shift reagent $\text{Eu}(\text{fod})_3$, has been used to detect and quantify the positional incorporation of low levels of ^2H in catalytically deuterated saturated carboxylic acid esters.

Sir: While ^1H NMR can be used effectively to determine the extent of ^2H incorporation in organic molecules, it has severe limitations. First, ^1H NMR requires that the molecule under study contain high concentrations of ^2H , since this technique can evaluate ^2H only by difference. Secondly, when ^2H is largely dispersed throughout a molecule even in relatively high total concentration, analysis becomes very difficult because of insignificant changes observed in the area of each of the dispersed ^1H resonances. As an alternate method, mass spectrometry can furnish information concerning the total level of isotopic incorporation; however, in most instances it cannot define the positional distribution of ^2H owing to ^2H - ^1H scrambling during the fragmentation process.

Although two orders of magnitude less sensitive in response to a magnetic field than ^1H , the ^2H nucleus is more amenable to Fourier transform methods.¹ Under complete proton decoupling conditions, ^2H resonances are normally observed as single resonances (no ^2H - ^2H spin coupling is observed), having chemical shifts closely corresponding to their ^1H counterparts.² Also, because of their relatively short longitudinal relaxation time, T_1 , multiple transients may be rapidly accumulated with short repetition times.¹ For example, a 100-mg sample of molecular weight of 200–300, containing 5% ^2H , which in magnetic response is equivalent to 0.05% ^1H , can yield an excellent quantitative spectrum within 0.5 h from 300 transients (repetition time only 5 s and a pulse angle of 60°).

^2H NMR in the presence^{2,3} and absence^{4,5} of lanthanide shift reagents can be used to examine positional substitution patterns in both static and rapidly exchanging ^1H , ^2H systems. Such a technique seemed amenable to our studies concerning the catalytic incorporation of ^2H into the saturated alkyl chains of carboxylic acids, since no other approach could quantify and evaluate the positional distribution of the low levels of widely dispersed ^2H . Typically, not more than a total of 29%, and in some cases as little as 2%, ^2H was incorporated into our representative samples. All ^2H spectra were obtained by use of a ^{31}P 10-mm probe of a JEOL FX-60Q NMR spectrometer,⁶ which normally operates at 24 MHz with a ^2H lock channel of 9.2 MHz. By reversing the offset/rf power modules and exchanging the lock and observation lines, we could lock

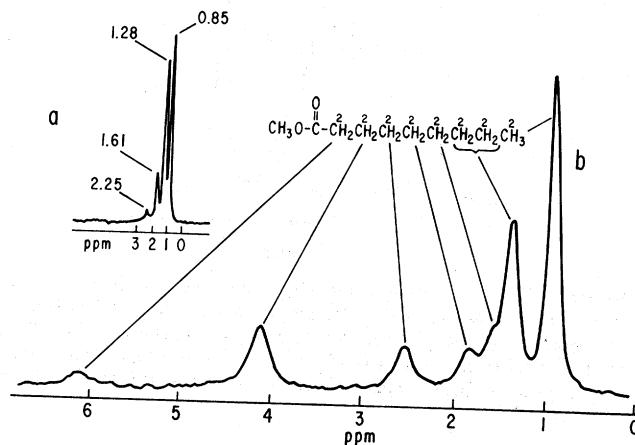


Figure 1. ^2H spectrum of: (a) methyl nonanoate, 255 transients, 4.4-s repetition rate, displayed spectral width = 500 Hz, 4K data points; (b) methyl nonanoate in the presence of $\text{Eu}(\text{fod})_3$ shift reagent, molar ratio of $\text{Eu}(\text{fod})_3$ /substrate = 0.7, 200 transients, 4.4-s repetition rate, displayed spectral width = 62.5 Hz. Total ^2H content = 29%.

Table I. Observed ^1H and ^2H Shifts (ppm) and ^2H Positional Distribution and Content^a

Table I. Observed ^1H and ^2H Shifts (ppm) and ^2H Positional Distribution and Content ^a										
		$\begin{array}{c} \text{O} \\ \parallel \\ \text{CH}_3\text{OCCH}-\text{CH}(\text{CH}_2)_x\text{R}'' \\ \text{R} \quad \text{R}' \end{array}$								total % ^2H content
	sample size, g	CH_3	2- CH_3	3- CH_3	$(\text{CH}_2)_x$	2- CH_2	3- CH_2	2-CH	3-CH	
^1H shifts (δ) ^b										
methyl nonanoate R = R' = H; R'' = CH ₃ ; x = 5		0.86			1.25	2.30	1.6 ^c			
methyl 2-methyloctanoate R = R'' = CH ₃ ; R' = H; x = 4		0.90	1.16		1.30			2.42		
methyl 3-methylpentanoate R = R'' = H; R' = CH ₃ ; x = 1		0.86		0.90	1.28	2.10			1.90	
dimethyl 1,7-heptanedioate R = R' = H; R'' = CO ₂ CH ₃ ; x = 5					1.30	2.30	1.50			
^2H Shifts (δ) ^d										
methyl nonanoate	0.085	0.85 (0.35)			1.28 (0.10) ^e (0.39) ^f	2.25 (0.03)	1.61 (0.13)			29
methyl 2-methyloctanoate	0.128	0.85 (0.61)	1.08 (0.24)		1.26 (0.15)			nf		8.7
methyl 3-methylpentanoate	0.103	0.90 (0.68)		0.90 (0.32)	nf	nf			nf	12.6
dimethyl 1,7-heptanedioate	0.096				1.30 ^g (0.39)	2.25 ^h (0.15)	1.50 ⁱ (0.46)			8.1

^a Content given as total percent deuterium incorporation determined by mass spectrometry. Numbers in parentheses represent the fractional distribution of ^2H found from the $\text{Eu}(\text{fod})_3$ spectrum. All proton shift assignments were in agreement with those reported in the Aldrich Catalog of proton NMR spectra. ^b Shifts were recorded in CCl_4 relative to internal Me_4Si . ^c Not clearly resolved at 60 MHz. ^d Shifts were recorded in CCl_4 and reported relative to 2% internal CDCl_3 referenced as 7.25 ppm. nf = no deuterium found at these positions. ^e Represents the 4- CH_2 position. ^f Represents 5- through 8- CH_2 positions. ^g Represents only the 5- CH_2 position. ^h Represents 2- and 8- CH_2 positions. ⁱ Represents 3-, 4-, 6-, and 7- CH_2 positions.

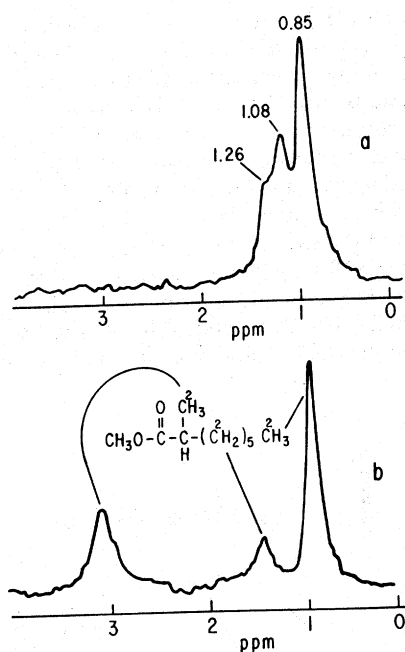


Figure 2. ^2H spectrum of: (a) methyl 2-methyloctanoate, 200 transients, 4.4-s repetition rate, displayed spectral width = 125 Hz, 8K data points; (b) methyl 2-methyloctanoate in the presence of $\text{Eu}(\text{fod})_3$ shift reagent, molar ratio of $\text{Eu}(\text{fod})_3/\text{substrate}$ = 0.25, 208 transients, 4.4-s repetition rate, displayed spectral width = 125 Hz. Total ^2H content = 8.7%.

onto the ^{31}P resonance of H_3PO_4 in a 1.8-mm capillary tube secured in the center of the 10-mm tube with a drilled out vortex plug and observe ^2H at 9.2 MHz.⁷

Table I lists the ^1H and the corresponding ^2H shifts observed for the methyl esters derived from catalytically deuterated carboxylic acids. Total percent ^2H incorporation into the esters was determined by mass spectrometry and the positional distribution by ^2H NMR. Figure 1a shows the ^2H spectrum of methyl nonanoate with 29% ^2H incorporation in the alkyl chain. In this spectrum the 2- and 3-methylene and terminal methyl ^2H resonances were clearly defined, whereas the remaining ^2H in the chain are seen as a single resonance. Although this spectrum was obtained at only 9.2 MHz, it illustrates the separation which is achievable from single line resonances in the absence of couplings. Note that the 3-position ^2H is readily distinguished, whereas the corresponding ^1H spectrum yields only a broad shoulder. A predominance of incorporation is apparent in the terminal methyl group, while the 2 position appears to have a low concentration. In the presence of shift reagent $[\text{Eu}(\text{fod})_3]$ (Figure 1b), the distribution of ^2H throughout the chain is easily ascertained (Table I). While such a separation was obtained for a ^1H spectrum of this ester in the presence of a shift reagent,⁸ it was not possible to quantify the low levels of ^1H depleted in each resonance peak. Figure 2a shows the ^2H spectrum of methyl 2-methyloctanoate, Figure 2b the corresponding spectrum in the presence of $\text{Eu}(\text{fod})_3$ shift reagent. The latter spectrum clearly demonstrates the presence of ^2H in positions 3 to 7 and the terminal and 2-position methyl groups of this carboxylic ester. No resonance corresponding to the 2-methine ^2H was observed. A predominance of incorporation is seen in the terminal methyl group resonances, which separate from the 2-methyl group under the influence of shift reagent (Figure 2b). Figures 3a and 3b illustrate the exclusive substitution of ^2H in the 3-methyl and terminal methyl groups of methyl 3-methylpentanoate and the dramatic resolution obtainable with the shift reagent. Dimethyl 1,7-heptanedioate exhibits

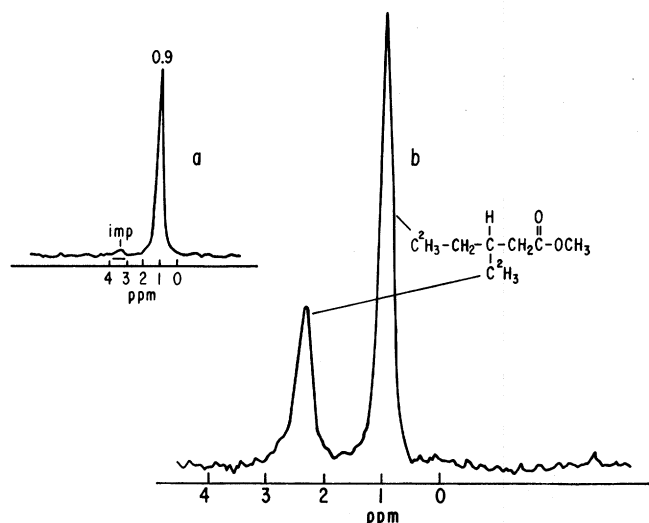


Figure 3. ^2H spectrum of: (a) methyl 3-methylpentanoate, 428 transients, 4.4-s repetition rate, displayed spectral width = 500 Hz, 8K data points; (b) methyl 3-methylpentanoate in the presence of $\text{Eu}(\text{fod})_3$ shift reagent, molar ratio of $\text{Eu}(\text{fod})_3$ /substrate = 0.25, 400 transients, 4.4-s repetition rate, displayed spectral width = 125 Hz. Total ^2H content = 12.6%.

a somewhat broadened spectrum in the presence of $\text{Eu}(\text{fod})_3$ because of the increased molecular weight and longer T_1

values of the double coordination site complex. However, the ^2H distribution for three distinct regions along the chain was still evident (Table I).

A full report concerning the catalytic procedures used for the ^2H exchange reactions into various compounds and their analyses by mass spectrometry and ^2H NMR spectroscopy will be the subject of future publications.

References and Notes

- (1) For a comprehensive review of the most recent work in ^2H NMR spectroscopy see: H. H. Mantsch, H. Saito, and I. C. P. Smith in "Progress in Nuclear Magnetic Resonance Spectroscopy", J. W. Emsley, J. Feeney, and L. H. Sutcliffe, Ed., Pergamon Press, London, 1977.
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- (3) A. L. Johnson, J. B. Stothers, and C. T. Tan, *Can. J. Chem.*, **52**, 4143 (1974).
- (4) T. P. Pitner, J. F. Whidby, and W. B. Edwards III, *Anal. Chem.*, **49**, 674 (1977).
- (5) D. E. Cane and S. L. Buchwald, *J. Am. Chem. Soc.*, **99**, 6132 (1977).
- (6) Reference to brand or firm name does not constitute endorsement by the U.S. Department of Agriculture over others of a similar nature not mentioned.
- (7) This modification is available through JEOL, Inc., Cranford, N.J. 07016.
- (8) D. B. Walters, *Anal. Chem. Acta*, **60**, 421 (1972).
- (9) JEOL Inc., Cranford, N.J. 07016.
- (10) Federal Research, Science and Education Administration, U.S. Department of Agriculture.

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